

## TOBACCO-SPECIFIC N-NITROSAMINES AND ARECA-DERIVED N-NITROSAMINES: CHEMISTRY, BIOCHEMISTRY, CARCINOGENICITY, AND RELEVANCE TO HUMANS

Dietrich Hoffmann, Klaus D. Brunnemann, Bogdan Prokopczyk,  
Mirjana V. Djordjevic

American Health Foundation, Valhalla, New York

Nicotine and the minor tobacco alkaloids give rise to tobacco-specific N-nitrosamines (TSNA) during tobacco processing and during smoking. Chemical-analytical studies led to the identification of seven TSNA in smokeless tobacco ( $\leq 25 \mu\text{g/g}$ ) and in mainstream smoke of cigarettes ( $1.3 \mu\text{g TSNA/cigarette}$ ). Indoor air polluted by tobacco smoke may contain up to  $24 \mu\text{g/L}$  of TSNA. In mice, rats, and hamsters, three TSNA, N'-nitrosornicotine (NNN), 4-(methylnitrosamino)-1-(3-pyridyl)-1-butane (NNK), and 4-(methylnitrosamino)-1-(3-pyridyl)-1-butanol (NNAL), are powerful carcinogens; two TSNA are moderately active as carcinogens; and two TSNA appear not to be carcinogenic. The TSNA are procarcinogens, agents that require metabolic activation. The active forms of the carcinogenic TSNA react with cellular components, including DNA, and with hemoglobin (Hb). The Hb adducts in chewers and smokers serve as biomarkers for the uptake and metabolic activation of carcinogenic TSNA and the urinary excretion of NNAL as free alcohol and as glucuronide for the uptake of TSNA. The review presents evidence that strongly supports the concept that TSNA contribute to the increased risk for cancer of the upper digestive tract in tobacco chewers and for the increased risk of lung cancer, especially pulmonary adenocarcinoma, in smokers. The high incidence of cancer of the upper digestive tract especially among men on the Indian subcontinent has been causally associated with chewing of betel quid mixed with tobacco. In addition to the TSNA, the betel quid chewers are exposed to four N-nitrosamines that are formed during chewing from the Areca alkaloids, two of these N-nitrosamines are carcinogens. The article also reviews approaches toward the reduction of the carcinogenic potency of smokeless tobacco, betel quid-tobacco mixtures, and cigarette smoke. Although the safest way to reduce the risk for tobacco-related cancers is to refrain from chewing and smoking, modifications of smokeless tobacco and of cigarettes are indicated to lead to less toxic products. Another more recent approach for reducing the carcinogenic effect of tobacco products is the application of chemopreventive agents, primarily of micronutrients. Future aspects in tobacco carcinogenesis, especially as it relates to TSNA, are expected in the field of molecular biochemistry and in biomarker studies, with the goal of identifying those tobacco and betel quid chewers and tobacco smokers who are at especially high risk for cancer.

Dedicated to Prof. Dr. Rudolf Preussmann on the occasion of his 65th birthday.

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Address correspondence to Dietrich Hoffmann, American Health Foundation, 1 Dana Road, Valhalla, NY 10595.